HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OPANA® ER safely and effectively. See full prescribing information for OPANA® ER.

OPANA® ER (oxymorphone hydrochloride) Extended-Release tablets, CII

Initial U.S. Approval: 1959

WARNING: POTENTIAL FOR ABUSE, IMPORTANCE OF PROPER PATIENT SELECTION AND LIMITATIONS OF USE

See full prescribing information for complete boxed warning.

- **OPANA ER contains oxymorphone which is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to other opioid analgesics. (9)**
- **Oxymorphone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OPANA ER in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. (9)**
- **OPANA ER is NOT intended for use as an as needed analgesic. (1)**
- **OPANA ER tablets are to be swallowed whole and are not to be cut, broken, chewed, dissolved, or crushed as this leads to rapid release and absorption of a potentially fatal dose of oxymorphone. (2)**
- **Patients must not consume alcoholic beverages, prescription or non-prescription medications containing alcohol. Co-ingestion of alcohol with OPANA ER may result in a potentially fatal overdose of oxymorphone. (2)**

----------INDICATIONS AND USAGE----------

- OPANA ER is an opioid agonist indicated for the relief of moderate to severe pain in patients requiring continuous around-the-clock opioid treatment for an extended period of time. (1)
- Not intended for use as an as needed analgesic. Not indicated in the immediate post-operative period or if the pain is mild or not expected to persist for an extended period of time. (1)

----------DOSAGE AND ADMINISTRATION----------

- Administer on an empty stomach, at least 1 hour prior to or 2 hours after eating. (2.2)
- Symmetrical, every 12 h dosing is appropriate for the majority of patients. (2.1)
- Opioid-Naïve Patients: Initiate treatment with 5 mg every 12 hours. (2.2)
- Opioid-Experienced Patients: Ratios as a guide to convert only from other opioids to OPANA ER. (2.2)
- Individualize treatment; titrate to effective and tolerable dose. (2.1)
- Don't stop abruptly (9.3); taper gradually to stop treatment. (2.8)
- OPANA ER tablets should be taken one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth (2.1, 17)

----------DOSAGE FORMS AND STRENGTHS----------

- Extended-Release Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg (3)

----------CONTRAINDICATIONS----------

- Known hypersensitivity to oxymorphone, any other ingredients in OPANA ER, or morphine analogs. (4)
- Respiratory depression (4)
- Acute or severe bronchial asthma or hypercarbia (4)
- Paralytic ileus (4)
- Moderate or severe hepatic impairment (4)

----------WARNINGS AND PRECAUTIONS----------

See Boxed WARNINGS

- Respiratory depression: Increased risk in elderly, debilitated patients, and those suffering from conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve. (5.2)
- Misuse, abuse, and diversion: OPANA ER is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine. (5.3)
- CNS effects: Additive CNS-depressive effects when used in conjunction with alcohol, other opioids, or illicit drugs. (5.4)
- Head Injury: Effects may be markedly exaggerated. Administer OPANA ER with extreme caution. (5.5)
- Hypotensive effect: Increased risk with compromised ability to maintain blood pressure. Administer with caution to patients in circulatory shock. (5.6)
- Mild hepatic impairment: Use with caution and at lower doses due to higher plasma concentrations than in patients with normal hepatic function. (5.7)
- Prolonged gastric obstruction: May occur in patients with gastrointestinal obstruction. (5.9)
- Sphincter of Oddi: Administer with caution in patients with biliary tract disease. (5.11)
- Impaired mental/physical abilities: Caution must be used with potentially hazardous activities (5.12)

----------ADVERSE REACTIONS----------

Adverse reactions in ≥2% of oxymorphone ER-treated patients in placebo-controlled trials: nausea, constipation, dizziness, somnolence, vomiting, pruritus, headache, sweating increased, dry mouth, sedation, diarrhea, insomnia, fatigue, appetite decreased, and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Endo Pharmaceuticals Inc. at (1-800-462-3636) or FDA at 1-800 FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- CNS depressants: Increased risk of respiratory depression, hypotension, profound sedation, coma or death when combined with OPANA ER. When combined therapy with CNS depressant is contemplated, the dose of one or both agents should be reduced. (7.2)
- Mixed agonist/antagonist opioids (i.e., pentazocine, nalbuphine, and butorphanol): May reduce analgesic effect and/or precipitate withdrawal symptoms. (7.3)
- Cimetidine: Combination use with OPANA ER may precipitate confusion, disorientation, respiratory depression, apnea, seizures. (7.4)
- Anticholinergics: Concurrent use with OPANA ER may result in urinary retention and/or severe constipation, which may lead to paralytic ileus. (7.5)
- Monoamine oxidase inhibitors (MAOIs): Potentiate the action of opioids. OPANA ER should not be used in patients taking MAOIs or within 14 days of stopping such treatment. (7.6)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Geriatric Patients – OPANA ER should be used with caution in elderly patients. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA – approved Medication Guide

Revised: 12/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*****Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: POTENTIAL FOR ABUSE, IMPORTANCE OF PROPER PATIENT SELECTION AND LIMITATIONS OF USE

Potential for Abuse

OPANA ER contains oxymorphone, which is a morphine-like opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. (9)

Oxymorphone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OPANA ER in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. (9.2)

Proper Patient Selection

OPANA ER is an extended-release oral formulation of oxymorphone indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. (1)

Limitations of Use

OPANA ER is NOT intended for use as an as needed analgesic. (1)

OPANA ER tablets are to be swallowed whole and are not to be cut, broken, chewed, dissolved, or crushed. Taking cut, broken, chewed, dissolved, or crushed OPANA ER tablets leads to rapid release and absorption of a potentially fatal dose of oxymorphone. (2)

Patients must not consume alcoholic beverages, or prescription or non-prescription medications containing alcohol, while on OPANA ER therapy. The co-ingestion of alcohol with OPANA ER may result in increased plasma levels and a potentially fatal overdose of oxymorphone. (2)

1 INDICATIONS AND USAGE

OPANA ER is indicated for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.

Limitations of Usage
OPANA ER is not intended for use as an as needed analgesic.

OPANA ER is not indicated for pain in the immediate post-operative period if the pain is mild, or not expected to persist for an extended period of time.

OPANA ER is only indicated for post-operative use if the patient is already receiving the drug prior to surgery or if the post-operative pain is expected to be moderate or severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines).

2 DOSAGE AND ADMINISTRATION

2.1 Safe Administration Instructions

OPANA ER tablets must be swallowed whole and are not to be cut, broken, chewed, dissolved, or crushed. Taking cut, broken, chewed, dissolved, or crushed OPANA ER tablets leads to rapid release and absorption of a potentially fatal dose of oxymorphone.

Patients must not consume alcoholic beverages, or prescription or non-prescription medications containing alcohol, while on OPANA ER therapy. The co-ingestion of alcohol with OPANA ER may result in increased plasma levels and a potentially fatal overdose of oxymorphone.

OPANA ER tablets must be taken whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth *[see Patient Counseling Information (17)]*.

OPANA ER must be taken on an empty stomach, at least one hour prior to or two hours after eating *[see Clinical Pharmacology (12.3)]*.

While symmetric (same dose AM and PM), around-the-clock, every 12 hours dosing is appropriate for the majority of patients, some patients may benefit from asymmetric (different dose given in AM than in PM) dosing, tailored to their pain pattern. It is usually appropriate to treat a patient with only one extended-release opioid for around-the-clock therapy.

Selection of patients for treatment with OPANA ER should be governed by the same principles that apply to the use of other extended-release opioid analgesics *[see Indications and Usage (1)]*. Physicians should individualize treatment in every case, using non-opioid analgesics, opioids on an as needed basis, combination products, and chronic opioid therapy in a progressive plan of pain management such as outlined by the World Health Organization, the American Pain Society and the Federation of State Medical Boards Model Guidelines. Healthcare professionals should follow appropriate pain management principles of careful assessment and ongoing monitoring *[see Boxed Warning]*.

2.2 Initiating Therapy with OPANA ER

It is necessary to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. In the selection of the initial dose of OPANA ER, attention should be given to the following:

- total daily dose, potency and specific characteristics of the opioid the patient has been taking previously;
- relative potency estimate used to calculate the equivalent oxymorphone dose needed;
- patient's degree of opioid tolerance;
- age, general condition, and medical status of the patient;
- concurrent non-opioid analgesics and other medications;
- type and severity of the patient's pain;
- balance between pain control and adverse experiences;
- risk factors for abuse or addiction, including a prior history of abuse or addiction.

Once therapy is initiated, frequently assess pain relief and other opioid effects. Base the titration of the total daily OPANA ER dose upon the amount of supplemental opioid utilization, severity of the patient's pain, and the patient's ability to tolerate the opioid. Titrate dose to generally mild or no pain with the regular use of no more than two doses of supplemental analgesia, i.e. "rescue," per 24 hours, and tolerable side effects. Patients who experience breakthrough pain may require dosage adjustment.

If signs of excessive opioid-related adverse experiences are observed, the next dose may be reduced. If this adjustment leads to inadequate analgesia, a supplemental dose of immediate-release opioid, or a non-opioid analgesic may be administered. Adjust dosing to obtain an appropriate balance between pain relief and opioid-related adverse experiences. If significant adverse events occur before the therapeutic goal of mild or no pain is achieved, the events should be treated aggressively. If adverse events are adequately managed, continue upward titration to an acceptable level of pain control.

During periods of changing analgesic requirements, including initial titration, frequent contact is recommended between physician, other members of the healthcare team, the patient and the caregiver/family. Advise patients and caregivers/family members of the potential adverse reactions.

The dosing recommendations below, therefore, can only be considered as suggested approaches to what is actually a series of clinical decisions over time in the management of the pain of each individual patient.

Titrate dose to adequate pain relief (generally mild or no pain).

<u>Opioid-Naïve Patients</u>

The initial dose for patients who are not opioid-experienced and who are being initiated on chronic around-the-clock opioid therapy with OPANA ER is 5 mg every 12 hours. Thereafter, titrate the dose individually at increments of 5-10 mg every 12 hours every 3-7 days, to a level that provides adequate analgesia and tolerable side effects under the close supervision of the prescribing physician.

<u>Opioid-Experienced Patients</u>

Conversion from OPANA to OPANA ER
Patients receiving OPANA may be converted to OPANA ER by administering half the patient's total daily oral OPANA dose as OPANA ER, every 12 hours.

Conversion from Parenteral Oxymorphone to OPANA ER
Given OPANA ER's absolute oral bioavailability of approximately 10%, patients receiving parenteral oxymorphone may be converted to OPANA ER by administering 10 times the patient's total daily parenteral oxymorphone dose as OPANA ER in two equally divided doses (e.g., [IV dose x 10] divided by 2). Due to patient variability with regards to opioid analgesic response, upon conversion monitor patients closely to evaluate for adequate analgesia and side effects.

Conversion from Other Oral Opioids to OPANA ER
For conversion from other opioids to OPANA ER, physicians and other healthcare professionals are advised to refer to published relative potency information, keeping in mind that conversion ratios are only approximate.

The following table provides approximate equivalent doses, which may be used as a guideline for conversion. **The conversion ratios and approximate equivalent doses in this conversion table are only to be used for the conversion from current opioid therapy to OPANA ER.**

- In general, it is safest to start the OPANA ER therapy by administering 50% of the calculated total daily dose, calculated below, of OPANA ER (see conversion ratio table below) in 2 divided doses, every 12 hours. Gradually adjust the initial dose of OPANA ER until adequate pain relief and acceptable side effects have been achieved.

Calculating the total daily dose of OPANA ER:

Step 1 Calculate the total daily dose of the opioid.

Step 2 Multiply the total daily dose for the opioid by the conversion ratio in Table 1 to calculate the total daily oxymorphone dose.

Table 1: Oral Opioid Conversion Ratios to OPANA ER

Oral Opioid	Oral Conversion Ratio
Oxymorphone	1
Hydrocodone	0.5
Oxycodone	0.5
Methadone [a]	0.5
Morphine	0.333

Step 3 Adjust the total daily dose of oxymorphone for the individual patient.

Step 4 Divide the total daily oxymorphone dose in half to determine the OPANA ER dose to be administered every 12 hours.

- For patients on a regimen of mixed opioids, calculate the approximate oral oxymorphone dose for each opioid, sum the totals, and divide in half to estimate the total daily oxymorphone dose.
- The dose of OPANA ER can be gradually adjusted, preferably at increments of 10 mg every 12 hours every 3-7 days, until adequate pain relief and acceptable side effects have been achieved [*see Dosage and Administration (2.1*)].

[a]**It is extremely important to monitor all patients closely when converting from methadone to other opioid agonists including OPANA ER.** The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and accumulates in the plasma.

No dose adjustment for CYP 3A4 or 2C9 mediated drug-drug interactions is required *[see Clinical Pharmacology (12.3)]*.

2.3 Patients with Hepatic Impairment

Start patients with mild hepatic impairment with the lowest dose and titrated slowly while carefully monitoring side effects. OPANA ER is contraindicated in patients with moderate or severe hepatic impairment *[Warnings and Precautions (5.7) and Clinical Pharmacology (12.3)]*

2.4 Patients with Renal Impairment

There are 57% and 65% increases in oxymorphone bioavailability in patients with moderate and severe renal impairment, respectively *[see Clinical Pharmacology (12.3)]*. Accordingly, in patients with creatinine clearance rates less than 50 mL/min, start OPANA ER with the lowest dose and titrate slowly while carefully monitoring side effects.

2.5 Use with Central Nervous System Depressants

In patients who are concurrently receiving other central nervous system (CNS) depressants including sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, and alcohol, start OPANA ER at 1/3 to 1/2 of the usual dose because respiratory depression, hypotension, and profound sedation, coma or death may result *[see Warnings and Precautions (5.4) and Drug Interactions (7.2)]*.

Although no specific interaction between oxymorphone and monoamine oxidase inhibitors has been observed, OPANA ER is not recommended for use in patients who have received MAO inhibitors within 14 days [*see Drug Interactions (7.6)]*.

2.6 Geriatrics Patients

The steady-state plasma concentrations of oxymorphone are approximately 40% higher in elderly subjects than in young subjects. Exercise caution in the selection of the starting dose of OPANA ER for an elderly patient by starting at the low end of the dosing range and slowly titrating to adequate analgesia *[see Clinical Pharmacology (12.3) and Use in Specific Populations (8.5)]*.

2.7 Maintenance of Therapy

During chronic therapy with OPANA ER, periodically reassess the continued need for around-the-clock opioid therapy. Continue to assess patients for their clinical risks for opioid abuse, addiction, or diversion particularly with high-dose formulations. If patients need to titrate while on maintenance therapy, follow the same method outlined in *Initiating Therapy with OPANA ER.*

2. 8 Cessation of Therapy

When the patient no longer requires therapy with OPANA ER tablets, gradually taper doses to prevent signs and symptoms of withdrawal in the physically dependent patient.

3 DOSAGE FORMS AND STRENGTHS

The 5 mg dosage form is a pink, round, film-coated, biconvex extended-release tablet debossed with an “E” on one side and a “5” on the other side.

The 7.5 mg dosage form is a gray, round, film-coated, biconvex extended-release tablet debossed with an “E” on one side and a “7 ½” on the other side.

The 10 mg dosage form is a light orange, round, film-coated, biconvex extended-release tablet debossed with an “E” on one side and a “10” on the other side.

The 15 mg dosage form is a white, round, film-coated, biconvex extended-release tablet debossed with an "E" on one side and a "15" on the other side.

The 20 mg dosage form is a light green, round, film-coated, biconvex extended-release tablet debossed with an "E" on one side and a "20" on the other side.

The 30 mg dosage form is a red, round, film-coated, biconvex extended-release tablet debossed with an "E" on one side and a "30" on the other side.

The 40 mg dosage form is a light yellow to pale yellow, round, film-coated, biconvex extended-release tablet debossed with an "E" on one side and a "40" on the other side.

4 CONTRAINDICATIONS

OPANA ER is contraindicated in patients who have:

- known hypersensitivity to any of its components or the active ingredient, oxymorphone or with known hypersensitivity to morphine analogs such as codeine.
- significant respiratory depression
- acute or severe bronchial asthma or hypercarbia
- or are suspected of having paralytic ileus
- moderate and severe hepatic impairment *[see Clinical Pharmacology (12.3), Warnings and Precautions (5.7)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Information Essential for Safe Administration

OPANA ER tablets are to be swallowed whole, and are not to be cut, broken, chewed, crushed or dissolved. Taking cut, broken, chewed, dissolved, or crushed OPANA ER tablets could lead to the rapid release and absorption of a potentially fatal dose of oxymorphone *[see Boxed Warning]*.

Patients must not consume alcoholic beverages, or prescription or non-prescription medications containing alcohol, while on OPANA ER therapy. The co-ingestion of alcohol with OPANA ER may result in increased plasma levels and a potentially fatal overdose of oxymorphone *[see Pharmacokinetics (12.3)]*.

Instruct patients against use by individuals other than the patient for whom OPANA ER was prescribed, as such inappropriate use may have severe medical consequences, including death.

5.2 Respiratory Depression

Respiratory depression is the chief hazard of OPANA ER. Respiratory depression is a potential problem in elderly or debilitated patients as well as in those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may dangerously decrease pulmonary ventilation.

Administer OPANA ER with extreme caution to patients with conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve such as: asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, CNS depression or coma. In these patients, even usual therapeutic doses of oxymorphone may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea. Consider alternative non-opioid analgesics and use OPANA ER only under careful medical supervision at the lowest effective dose in such patients.

5.3 Misuse, Abuse and Diversion of Opioids

OPANA ER contains oxymorphone, a mu opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine. Opioid agonists are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Oxymorphone can be abused in a manner similar to other opioid agonists, legal or illicit. This issue should be considered when prescribing or dispensing oxymorphone in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OPANA ER tablets may be abused by crushing, chewing, snorting or injecting the product. These practices will result in the less controlled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death *[see Drug Abuse and Dependence (9)]*.

OPANA ER may be targeted for theft and diversion. Healthcare professionals should contact their State Medical Board, State Board of Pharmacy, or State Control Board for information on how to detect or prevent diversion of this product, and security requirements for storing and handling of OPANA ER.

Healthcare professionals should advise patients to store OPANA ER in a secure place, preferably locked and out of the reach of children and other non-caregivers.

Concerns about abuse, misuse, diversion and addiction should not prevent the proper management of pain.

5.4 Interactions with Alcohol and other CNS Depressants

Patients receiving other opioid analgesics, general anesthetics, phenothiazines or other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with oxymorphone may experience respiratory depression, hypotension, profound sedation, coma and death *[see Drug Interactions (7.2)]*. Avoid concurrent use of alcohol and OPANA ER *[see Pharmacokinetics (12.3)]*.

5.5 Use in Patients with Head Injury and Increased Intracranial Pressure

In the presence of head injury, intracranial lesions or a preexisting increase in intracranial pressure, the possible respiratory depressant effects of opioid analgesics and their potential to elevate cerebrospinal fluid pressure (resulting from vasodilation following CO_2 retention) may be markedly exaggerated. Furthermore, opioid analgesics can produce effects on papillary response and consciousness, which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

Administer OPANA ER with extreme caution to patients who may be particularly susceptible to the intracranial effects of CO_2 retention, such as those with evidence of increased intracranial pressure or impaired consciousness. Opioids may obscure the clinical course of a patient with a head injury and should be used only if clinically warranted.

5.6 Hypotensive Effect

OPANA ER may cause severe hypotension in a patient whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents that compromise vasomotor tone. Administer OPANA ER with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

5.7 Hepatic Impairment

A study of oxymorphone hydrochloride extended-release tablets in patients with hepatic disease indicated greater plasma concentrations than those with normal hepatic function *[see Clinical Pharmacology (12)]*. Use OPANA ER with caution in patients with mild impairment, starting with the lowest dose and titrating slowly while carefully monitoring for side effects *[see Dosage and Administration (2.3)]*. OPANA ER is contraindicated in patients with moderate or severe hepatic impairment.

5.8 Special Risk Groups

Use OPANA ER with caution in the following conditions: adrenocortical insufficiency (e.g., Addison's disease), prostatic hypertrophy or urethral stricture, severe impairment of pulmonary or renal function, and toxic psychosis.

Opioids may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures in some clinical settings.

5.9 Gastrointestinal Effects

OPANA ER decreases bowel motility. Opioids diminish propulsive peristaltic waves in the gastrointestinal tract. Monitor for decreased bowel motility in post-operative patients receiving opioids. The administration of
OPANA ER may obscure the diagnosis or clinical course in patients with acute abdominal conditions. OPANA ER is contraindicated in patients with paralytic ileus.

5.10 Ambulatory Surgery and Post-Operative Use

OPANA ER is not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain).

OPANA ER is only indicated for postoperative use in the patient if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate (see American Pain Society guidelines).

Patients who are already receiving OPANA ER as part of ongoing analgesic therapy may be safely continued on the drug if appropriate dosage adjustments are made considering the procedure, other drugs given, and the temporary changes in physiology caused by the surgical intervention.

5.11 Use in Pancreatic/Biliary Tract Disease

OPANA ER, like other opioids, may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis.

5.12 Driving and Operating Machinery

Opioid analgesics, including OPANA ER, may impair the mental and physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Respiratory depression *[see Warnings and Precautions (5.2)]*
- Misuse and abuse *[see Warning and Precautions (5.3) and Drug Abuse and Dependence (9)]*
- CNS depressant effects *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of oxymorphone hydrochloride extended-release tablets was evaluated in a total of 2011 patients in controlled clinical trials. The clinical trials consisted of patients with moderate to severe chronic non-malignant pain, cancer pain, and post surgical pain.

Tables 1 and 2 list the most frequently occurring adverse reactions (in at least 5% of patients) from the placebo-controlled trials in patients with low back pain.

Table 1:Treatment-Emergent Adverse Events Reported in ≥5% of Patients During the Open-Label Titration Period and Double-Blind Treatment Period by Preferred Term —Number (%) of Treated Patients (12-Week Study In Opioid-Naïve Patients with Low Back Pain)

	Open-Label Titration Period	Double-Blind Treatment Period	
	Oxymorphone Hydrochloride Extended-Release Tablets	Oxymorphone Hydrochloride Extended-Release Tablets	Placebo
Preferred Term	**(N = 325)**	**(N = 105)**	**(N = 100)**
Constipation	26%	7%	1%
Somnolence	19%	2%	0%
Nausea	18%	11%	9%
Dizziness	11%	5%	3%
Headache	11%	4%	2%
Pruritus	7%	3%	1%

Table 2. Treatment-Emergent Adverse Events Reported in ≥5% of Patients During the Open-Label Titration Period and Double-Blind Treatment Period by Preferred Term — Number (%) of Treated Patients (12-Week Study In Opioid-Experienced Patients with Low Back Pain)

	Open-Label Titration Period	Double-Blind Treatment Period	
	Oxymorphone Hydrochloride Extended-Release Tablets	Oxymorphone Hydrochloride Extended-Release Tablets	Placebo
Preferred Term	**(N = 250)**	**(N = 70)**	**(N = 72)**
Nausea	20%	3%	1%
Constipation	12%	6%	1%
Headache	12%	3%	0%
Somnolence	11%	3%	0%
Vomiting	9%	0%	1%
Pruritus	8%	0%	0%
Dizziness	6%	0%	0%

The following table lists adverse reactions that were reported in at least 2% of patients in placebo-controlled trials (N=5).

Table 3: Adverse Reactions Reported in Placebo-Controlled Clinical Trials with Incidence ≥2% in Patients Receiving Oxymorphone Hydrochloride Extended-Release Tablets.

MedDRA Preferred Term	Oxymorphone Hydrochloride Extended-Release Tablets (N=1259)	Placebo (N=461)
Nausea	33%	13%
Constipation	28%	13%
Dizziness (Excl Vertigo)	18%	8%
Somnolence	17%	2%
Vomiting	16%	4%
Pruritus	15%	8%
Headache	12%	6%
Sweating increased	9%	9%

Dry mouth	6%	<1%
Sedation	6%	8%
Diarrhea	4%	6%
Insomnia	4%	2%
Fatigue	4%	1%
Appetite decreased	3%	<1%
Abdominal pain	3%	2%

The **common** (≥1% to <10%) adverse drug reactions reported at least once by patients treated with oxymorphone hydrochloride extended-release tablets in the clinical trials organized by MedDRA's (Medical Dictionary for Regulatory Activities) System Organ Class and not represented in Table 1:

Eye disorders: vision blurred
Gastrointestinal disorders: diarrhea, abdominal pain, dyspepsia
*General disorders and administration site conditions***:** dry mouth, appetite decreased, fatigue, lethargy, weakness, pyrexia, dehydration, weight decreased, edema
Nervous system disorders: insomnia
Psychiatric disorders: anxiety, confusion, disorientation, restlessness, nervousness, depression
Respiratory, thoracic and mediastinal disorders: dyspnea
Vascular disorders: flushing and hypertension

Other **less common** adverse reactions known with opioid treatment that were seen <1% in the oxymorphone hydrochloride extended-release tablets trials include the following:

Bradycardia, palpitation, syncope, tachycardia, postural hypotension, miosis, visual disturbance, abdominal distention, ileus, feeling jittery, hot flashes, allergic reactions, hypersensitivity, urticaria, oxygen saturation decreased, central nervous system depression, depressed level of consciousness, agitation, dysphoria, euphoric mood, hallucination, mental impairment, mental status changes, difficult micturition, urinary retention, hypoxia, respiratory depression, respiratory distress, respiratory rate decreased, clamminess, dermatitis, hypotension.

7 DRUG INTERACTIONS

7.1 Drug-Drug Interactions

Oxymorphone is highly metabolized principally in the liver and undergoes reduction or conjugation with glucuronic acid to form both active and inactive metabolites *[see Clinical Pharmacology (12.3)]*. Clinical drug interaction studies with oxymorphone hydrochloride extended-release tablets showed no induction of CYP450 3A4 or 2C9 enzyme activity, indicating that no dose adjustment for CYP 3A4- or 2C9-mediated drug-drug interactions is required *[see Clinical Pharmacology (12.3)]*.

7.2 Use with CNS Depressants

The concomitant use of other CNS depressants including sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and alcohol may produce additive CNS depressant effects. OPANA ER should be started at 1/3 to 1/2 of the usual dose in patients who are concurrently receiving other central nervous system depressants because respiratory depression, hypotension, and profound sedation, coma and death may result, and titrated slowly as necessary for adequate pain relief.

When combined therapy with any of the above medications is considered, the dose of one or both agents should be reduced *[see Dosage and Administration (2.5) and Warnings and Precautions (5.4)]*.

7.3 Interactions with Mixed Agonist/Antagonist Opioid Analgesics

Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol, or buprenorphine) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic, such as OPANA ER. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of OPANA ER and/or may precipitate withdrawal symptoms.

7.4 Cimetidine

CNS side effects have been reported (e.g., confusion, disorientation, respiratory depression, apnea, seizures) following coadministration of cimetidine with opioid analgesics; a causal relationship has not been established.

7.5 Anticholinergics

Anticholinergics or other medications with anticholinergic activity when used concurrently with opioid analgesics including OPANA ER may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

7.6 MAO Inhibitors

OPANA ER is not recommended for use in patients who have received MAO inhibitors within 14 days, because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics. No specific interaction between oxymorphone and MAO inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

The safety of using oxymorphone in pregnancy has not been established with regard to possible adverse effects on fetal development. The use of OPANA ER in pregnancy, in nursing mothers, or in women of child-bearing potential requires that the possible benefits of the drug be weighed against the possible hazards to the mother and the child.

Prolonged use of opioid analgesics including OPANA ER during pregnancy may cause fetal-neonatal physical dependence.

Teratogenic Effects

Pregnancy Category C

There are no adequate and well-controlled studies of oxymorphone in pregnant women. OPANA ER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus *[see Use in Specific Populations (8.2)]*.

Oxymorphone hydrochloride administration did not cause malformations at any doses evaluated during developmental toxicity studies in rats (≤25 mg/kg/day) or rabbits (≤50 mg/kg/day). These doses are ~3-fold and ~12-fold the human dose of 40 mg every 12 hours, based on body surface area. There were no developmental effects in rats treated with 5 mg/kg/day or rabbits treated with 25 mg/kg/day. Fetal weights were reduced in rats and rabbits given doses of ≥10 mg/kg/day and 50 mg/kg/day, respectively. These doses are ~1.2-fold and ~12-fold the human dose of 40 mg every 12 hours based on body surface area, respectively. There were no effects of oxymorphone hydrochloride on intrauterine survival in rats at doses ≤25 mg/kg/day, or rabbits at ≤50 mg/kg/day in these studies (see Non-teratogenic Effects, below). In a study that was conducted prior to the establishment of Good Laboratory Practices (GLP) and not according to current recommended methodology, a single subcutaneous injection of oxymorphone hydrochloride on gestation day 8 was reported to produce malformations in offspring of hamsters that received 15.5-fold the human dose of 40 mg every 12 hours based on body surface area. This dose also produced 20% maternal lethality.

Non-teratogenic Effects

Oxymorphone hydrochloride administration to female rats during gestation in a pre- and postnatal developmental toxicity study reduced mean litter size (18%) at a dose of 25 mg/kg/day, attributed to an increased incidence of stillborn pups. An increase in neonatal death occurred at ≥5 mg/kg/day. Post-natal survival of the pups was reduced throughout weaning following treatment of the dams with 25 mg/kg/day. Low pup birth weight and decreased postnatal weight gain occurred in pups born to oxymorphone-treated female rats given a dose of 25 mg/kg/day. This dose is ~3-fold higher than the human dose of 40 mg every 12 hours on a body surface area basis.

8.2 Labor and Delivery

Opioids cross the placenta and may produce respiratory depression in neonates. OPANA ER is not recommended for use in women during and immediately prior to labor, when use of shorter acting analgesics or other analgesic techniques are more appropriate. Occasionally, opioid analgesics may prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. However this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor.

Neonates whose mothers received opioid analgesics during labor should be observed closely for signs of respiratory depression. A specific opioid antagonist, such as naloxone or nalmefene, should be available for reversal of opioid-induced respiratory depression in the neonate.

Upon delivery from a mother who received opioids for a long period of time, neonatal withdrawal may occur. Symptoms usually appear during the first days of life and may include convulsions, irritability, excessive crying, tremors, hyperactive reflexes, fever, vomiting, diarrhea, sneezing, yawning, and increased respiratory rate.

8.3 Nursing Mothers

It is not known whether oxymorphone is excreted in human milk. Because many drugs, including some opioids, are excreted in human milk, caution should be exercised when OPANA ER is administered to a nursing woman. Infants exposed to OPANA ER through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breast-fed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.4 Pediatric Use

Safety and effectiveness of OPANA ER in pediatric patients below the age of 18 years have not been established.

8.5 Geriatric Use

OPANA ER should be used with caution in elderly patients *[see Clinical Pharmacology 12.3)]*.

Of the total number of subjects in clinical studies of extended-release oxymorphone tablets, 27% were 65 and over, while 9% were 75 and over. No overall differences in effectiveness were observed between these subjects and younger subjects. There were several adverse events that were more frequently observed in subjects 65 and over compared to younger subjects. These adverse events included dizziness, somnolence, confusion, and nausea.

8.6 Hepatic Impairment

In a PK study of extended-release oxymorphone tablets, patients with mild hepatic impairment were shown to have an increase in bioavailability of 1.6 fold. Use OPANA ER with caution in patients with mild impairment. Start these patients on the lowest dose and titrate slowly while carefully monitoring for side effects. OPANA ER is contraindicated for patients with moderate and severe hepatic impairment *[see Contraindications (4), Warnings and Precautions (5.7), and Dosage and Administration (2.3)]*.

8.7 Renal Impairment

In a PK study of extended-release oxymorphone tablets, patients with moderate to severe renal impairment were shown to have an increase in bioavailability ranging from 57-65% *[see Clinical Pharmacology (12.3)]*. Start these patients with the lowest dose of OPANA ER and titrate slowly while monitored for side effects *[see Dosage and Administration (2.4)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

OPANA ER contains oxymorphone, a mu agonist and a Schedule II controlled substance with an abuse liability similar to morphine and other opioids. Oxymorphone can be abused and is subject to criminal diversion *[see Warning and Precautions (5.3)]*.

9.2 Abuse

All patients treated with opioids including OPANA ER require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. Addiction is characterized by one or more of the following: impaired control over drug use, compulsive use, use for non-medical purposes, and continued use despite harm. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common.

"Drug seeking" behavior is very common to addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of loss of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. OPANA ER, like other opioids, may be diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

OPANA ER is intended for oral use only. Abuse of OPANA ER poses a risk of overdose and death. This risk is increased with concurrent abuse of OPANA ER with alcohol and other substances. Parenteral drug abuse is commonly associated with transmission of infectious disease such as hepatitis and HIV.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

9.3 Dependence

Opioid analgesics may cause physical dependence. Physical dependence results in withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an opioid antagonist or mixed opioid agonist/antagonist agent. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, buprenorphine, nalbuphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). The development of physical dependence and tolerance is not unusual during chronic opioid therapy.

OPANA ER should not be abruptly discontinued *[see Dosage and Administration (2.8)]*. If OPANA ER is abruptly discontinued in a physically-dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms *[see Use in Specific Populations (8.1, 8.2)]*.

10 OVERDOSAGE

10.1 Symptoms

Acute overdosage with OPANA ER is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor

or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils and sometimes bradycardia and hypotension. In some cases, apnea, circulatory collapse, cardiac arrest and death may occur.

OPANA ER may cause miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations *[see Clinical Pharmacology (12.2)]*.

10.2 Treatment

In the treatment of OPANA ER overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression that may result from overdosage or unusual sensitivity to opioids including OPANA ER. Nalmefene is an alternative pure opioid antagonist, which may be administered as a specific antidote to respiratory depression resulting from opioid overdose. Since the duration of action of OPANA ER may exceed that of the antagonist, keep the patient under continued surveillance and administer repeated doses of the antagonist according to the antagonist labeling as needed to maintain adequate respiration.

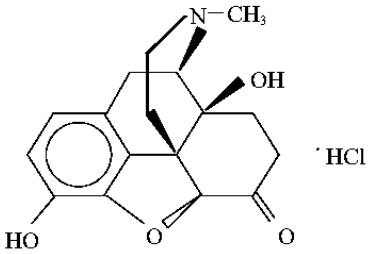
In patients receiving OPANA ER, opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression. Administer opioid antagonists cautiously to persons who are known, or suspected to be, physically dependent on any opioid agonist including OPANA ER. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. If respiratory depression is associated with muscular rigidity, administration of a neuromuscular blocking agent may be necessary to facilitate assisted or controlled ventilation. Muscular rigidity may also respond to opioid antagonist therapy.

11 DESCRIPTION

OPANA ER (oxymorphone hydrochloride) extended-release tablet is a semi-synthetic opioid analgesic supplied in 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg tablet strengths for oral administration. The tablet strength describes the amount of oxymorphone hydrochloride per tablet. The tablets contain the following inactive ingredients: hypromellose, polyethylene oxide, polyethylene glycol, α-tocopherol, citric acid, polyvinyl alcohol, titanium dioxide, macrogol and talc. In addition, the 5 mg, 7.5 mg and 30 mg tablets contain iron oxide red. The 7.5 mg tablets contain iron oxide black, and iron oxide yellow. The 10 mg tablets contain FD&C yellow No. 6. The 20 mg tablets contain FD&C blue No. 1, FD&C yellow No. 6, and D&C yellow No. 10. The 40 mg tablets contain FD&C yellow No. 6, and D&C yellow No. 10.

Chemically, oxymorphone hydrochloride is 4, 5α -epoxy-3, 14-dihydroxy-17-methylmorphinan-6-one hydrochloride, a white or slightly off-white, odorless powder, which is sparingly soluble in alcohol and very slightly soluble in ether, but freely soluble in water. The molecular weight of oxymorphone hydrochloride is 337.80. The pKa1 and pKa2 of oxymorphone at 37°C are 8.17 and 9.54, respectively. The octanol/aqueous partition coefficient at 37°C and pH 7.4 is 0.98.

The structural formula for oxymorphone hydrochloride is as follows:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Oxymorphone, a pure opioid agonist, is relatively selective for the mu receptor, although it can interact with other opioid receptors at higher doses.

The precise mechanism of analgesia, the principal therapeutic action of oxymorphone, is unknown. Specific central nervous system (CNS) opiate receptors and endogenous compounds with morphine-like activity have been identified throughout the brain and spinal cord and are likely to play a role in the expression and perception of analgesic effects. In addition, opioid receptors have also been identified within the peripheral nervous system (PNS). The role that these receptors play in these drugs' analgesic effects is unknown.

12.2 Pharmacodynamics

Concentration-Efficacy Relationships

The minimum effective plasma concentration of oxymorphone for analgesia varies widely among patients, especially among patients who have been previously treated with agonist opioids. As a result, individually titrate patients to achieve a balance between therapeutic and adverse effects. The minimum effective analgesic concentration of oxymorphone for any individual patient may increase over time due to an increase in pain, progression of disease, development of a new pain syndrome and/or potential development of analgesic tolerance.

Concentration-Adverse Experience Relationships

There is a general relationship between increasing opioid plasma concentration and increasing frequency of adverse experiences such as nausea, vomiting, CNS effects, and respiratory depression.

As with all opioids, the dose of OPANA ER must be individualized *[see Dosage and Administration (2.1)]*. The effective analgesic dose for some patients will be too high to be tolerated by other patients.

Effects on the Central Nervous System (CNS)

The principal therapeutic action of oxymorphone is analgesia. In common with other opioids, oxymorphone causes respiratory depression, in part by a direct effect on the brainstem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation. Opioids depress the cough reflex by direct effect on the cough center in the medulla.

Oxymorphone cause miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations *[see Overdosage (10.1)]*. Other therapeutic effects of oxymorphone include anxiolysis, euphoria and feeling of relaxation.

In addition to analgesia, the widely diverse effects of oxymorphone include drowsiness, changes in mood, decreased gastrointestinal motility, nausea, vomiting, and alterations of the endocrine and autonomic nervous system *[see Clinical Pharmacology (12.1)]*.

Effects on the Gastrointestinal Tract and on Other Smooth Muscle
Gastric, biliary and pancreatic secretions are decreased by oxymorphone. Oxymorphone causes a reduction in motility and is associated with an increase in tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm. The end result may be constipation. Oxymorphone can cause a marked increase in biliary tract pressure as a result of spasm of the sphincter of Oddi, and transient elevations in serum amylase. Oxymorphone may also cause spasm of the sphincter of the urinary bladder.

Cardiovascular System Effects
Opioids produce peripheral vasodilation which may result in orthostatic hypotension. Release of histamine can occur and may contribute to opioid-induced hypotension. Manifestations of histamine release may include orthostatic hypotension, pruritus, flushing, red eyes, and sweating. Animal studies have shown that oxymorphone has a lower propensity to cause histamine release than other opioids.

Endocrine System Effects
Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon in humans and other species, rats and dogs. Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids.

Immune System Effects
Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown.

12.3 Pharmacokinetics
Absorption
The absolute oral bioavailability of oxymorphone is approximately 10%.

Steady-state levels are achieved after three days of multiple dose administration. Under both single-dose and steady-state conditions, dose proportionality has been established for the 5 mg, 10 mg, 20 mg, and 40 mg doses of oxymorphone hydrochloride extended-release tablets, for both peak plasma levels (C_{max}) and extent of absorption (AUC) (see Table 4).

Table 4: Mean (±SD) Oxymorphone Hydrochloride Extended-Release Tablets Pharmacokinetic Parameters

Regimen	Dosage	C_{max} (ng/mL)	AUC (ng·hr/mL)	$T_{½}$ (hr)
Single Dose	5 mg 10 mg 20 mg 40 mg	0.27±0.13 0.65±0.29 1.21±0.77 2.59±1.65	4.54±2.04 8.94±4.16 17.81±7.22 37.90±16.20	11.30±10.81 9.83±5.68 9.89±3.21 9.35±2.94
Multiple Dose[a]	5 mg 10 mg 20 mg 40 mg	0.70±0.55 1.24±0.56 2.54±1.35 4.47±1.91	5.60±3.87 9.77±3.52 19.28±8.32 36.98±13.53	NA NA NA NA

NA = not applicable
[a] Results after 5 days of q12h dosing.

Food Effect
Two studies examined the effect of food on the bioavailability of single doses of 20 and 40 mg of oxymorphone hydrochloride extended-release tablets in healthy volunteers. In both studies, after the

administration of oxymorphone hydrochloride extended-release tablets, the C_{max} was increased by approximately 50% in fed subjects compared to fasted subjects. A similar increase in C_{max} was also observed with oxymorphone solution.

The AUC was unchanged in one study and increased by approximately 18% in the other study in fed subjects following the administration of oxymorphone hydrochloride extended-release tablets. Examination of the AUC suggests that most of the difference between fed and fasting conditions occurs in the first four hours after dose administration. After oral dosing with a single dose of 40 mg, a peak oxymorphone plasma level of 2.8 ng/ml is achieved at 1 hour in fasted subjects and a peak of 4.25 ng/ml is achieved at 2 hours in fed subjects and that beyond the 12 hour time point, there is very little difference in the curves. As a result, OPANA ER should be dosed at least one hour prior to or two hours after eating [*see Dosage and Administration (2.2)]*.

Ethanol Effect

In Vivo Oxymorphone Hydrochloride Extended-Release Tablets Formulation-Alcohol Interaction

Although *in vitro* studies have demonstrated that oxymorphone hydrochloride extended-release tablets do not release oxymorphone more rapidly in 500 mL of 0.1N HCl solutions containing ethanol (4%, 20%, and 40%), there is an *in vivo* interaction with alcohol. An *in vivo* study examined the effect of alcohol (40%, 20%, 4% and 0%) on the bioavailability of a single dose of 40 mg of oxymorphone hydrochloride extended-release tablets in healthy, fasted volunteers. The results showed that the oxymorphone mean AUC was 13% higher (not statistically significant) after co-administration of 240 mL of 40% alcohol. The AUC was essentially unaffected in subjects following the co-administration of oxymorphone hydrochloride extended-release tablets and ethanol (240 mL of 20% or 4% ethanol).

There was a highly variable effect on C_{max} with concomitant administration of alcohol and oxymorphone hydrochloride extended-release tablets. The change in C_{max} ranged from a decrease of 50% to an increase of 270% across all conditions studied. Following concomitant administration of 240 mL of 40% ethanol the C_{max} increased on average by 70% and up to 270% in individual subjects. Following the concomitant administration of 240 mL of 20% ethanol, the C_{max} increased on average by 31% and up to 260% in individual subjects. Following the concomitant administration of 240 mL of 4 % ethanol, the C_{max} increased 7% on average and by as much as 110% for individual subjects. After oral dosing with a single dose of 40 mg in fasted subjects, the mean peak oxymorphone plasma level is 2.4 ng/mL and the median T_{max} is 2 hours. Following co-administration of oxymorphone hydrochloride extended-release tablets and alcohol (240 mL of 40% ethanol) in fasted subjects, the mean peak oxymorphone level is 3.9 ng/mL and the median T_{max} is 1.5 hours (range 0.75 – 6 hours).

Co-administration of OPANA ER and ethanol must be avoided.

OPANA ER may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression because respiratory depression, hypotension, and profound sedation, coma, or death may result.

Distribution

Formal studies on the distribution of oxymorphone in various tissues have not been conducted. Oxymorphone is not extensively bound to human plasma proteins; binding is in the range of 10% to 12%.

Metabolism

Oxymorphone is highly metabolized, principally in the liver, and undergoes reduction or conjugation with glucuronic acid to form both active and inactive metabolites. The two major metabolites of oxymorphone are oxymorphone-3-glucuronide and 6-OH-oxymorphone. The mean plasma AUC for oxymorphone-3-glucuronide is approximately 90-fold higher than the parent compound. The pharmacologic activity of the glucuronide metabolite has not been evaluated. 6-OH-oxymorphone has been shown in animal studies to have analgesic bioactivity. The mean plasma 6-OH-oymorphone AUC is approximately 70% of the oxymorphone AUC following single oral doses, but is essentially equivalent to the parent compound at steady-state.

Excretion

Because oxymorphone is extensively metabolized, <1% of the administered dose is excreted unchanged in the urine. On average, 33% to 38% of the administered dose is excreted in the urine as oxymorphone-3-glucuronide and 0.25% to 0.62% excreted as 6-OH-oxymorphone in subjects with normal hepatic and renal function. In animals given radiolabeled oxymorphone, approximately 90% of the administered radioactivity was recovered within 5 days of dosing. The majority of oxymorphone-derived radioactivity was found in the urine and feces

Pharmacokinetics in Special Populations

Elderly

The steady-state plasma concentrations of oxymorphone, 6-OH-oxymorphone, and oxymorphone-3-glucuronide are approximately 40% higher in elderly subjects (≥ 65 years of age) than in young subjects (18 to 40 years of age). On average, age greater than 65 years was associated with a 1.4-fold increase in oxymorphone AUC and a 1.5-fold increase in C_{max}. This observation does not appear related to a difference in body weight, metabolism, or excretion of oxymorphone *[see Use in Specific Populations (8.5)]*.

Gender

The effect of gender was evaluated following single- and multiple-doses of oxymorphone hydrochloride extended-release tablets in male and female adult volunteers. There was a consistent tendency for female subjects to have slightly higher AUC_{ss} and C_{max} values than male subjects; however, gender differences were not observed when AUC_{ss} and C_{max} were adjusted by body weight.

Hepatic Impairment

The liver plays an important role in the pre-systemic clearance of orally administered oxymorphone. Accordingly, the bioavailability of orally administered oxymorphone may be markedly increased in patients with moderate to severe liver disease. The disposition of oxymorphone was compared in 6 patients with mild, 5 patients with moderate, and one patient with severe hepatic impairment and 12 subjects with normal hepatic function. The bioavailability of oxymorphone was increased by 1.6-fold in patients with mild hepatic impairment and by 3.7-fold in patients with moderate hepatic impairment. In one patient with severe hepatic impairment, the bioavailability was increased by 12.2-fold. The half-life of oxymorphone was not significantly affected by hepatic impairment.

Renal Impairment

Data from a pharmacokinetic study involving 24 patients with renal dysfunction show an increase of 26%, 57%, and 65% in oxymorphone bioavailability in mild (creatinine clearance 51-80 mL/min; n=8), moderate (creatinine clearance 30-50 mL/min; n=8), and severe (creatinine clearance <30 mL/min; n=8) patients, respectively, compared to healthy controls.

Drug-Drug Interactions

In vitro studies revealed little to no biotransformation of oxymorphone to 6-OH-oxymorphone by any of the major cytochrome P450 (CYP P450) isoforms at therapeutically relevant oxymorphone plasma concentrations.

No inhibition of any of the major CYP P450 isoforms was observed when oxymorphone was incubated with human liver microsomes at concentrations of ≤ 50 μM. An inhibition of CYP3A4 activity occurred at oxymorphone concentrations ≥150 μM. Therefore, it is not expected that oxymorphone, or its metabolites will act as inhibitors of any of the major CYP P450 enzymes *in vivo*.

Increases in the activity of the CYP 2C9 and CYP 3A4 isoforms occurred when oxymorphone was incubated with human hepatocytes. However, clinical drug interaction studies with oxymorphone hydrochloride extended-release tablets showed no induction of CYP450 3A4 or 2C9 enzyme activity, indicating that no dose adjustment for CYP 3A4- or 2C9-mediated drug-drug interactions is required.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies have been completed to evaluate the carcinogenic potential of oxymorphone in both Sprague-Dawley rats and CD-1 mice. Oxymorphone HCl was administered to Sprague-Dawley rats (2.5, 5, and 10 mg/kg/day in males and 5, 10, and 25 mg/kg/day in females) for 2 years by oral gavage. The systemic drug exposure (AUC ng•h/mL) at the 10 mg/kg/day in male rats was 0.34-fold and at the 25 mg/kg/day dose in female rats was 1.5-fold the human exposure at a dose of 260 mg/day. No evidence of carcinogenic potential was observed in rats. Oxymorphone was administered to CD-1 mice (10, 25, 75 and 150 mg/kg/day) for 2 years by oral gavage. The systemic drug exposure (AUC ng•h/mL) at the 150 mg/kg/day dose in mice was 14.5-fold (in males) and 17.3-fold (in females) times the human exposure at a dose of 260 mg/day. No evidence of carcinogenic potential was observed in mice.

Mutagenesis

Oxymorphone hydrochloride was not mutagenic when tested in the *in vitro* bacterial reverse mutation assay (Ames test) at concentrations of ≤5270 μg/plate, or in an *in vitro* mammalian cell chromosome aberration assay performed with human peripheral blood lymphocytes at concentrations ≤5000 μg/ml with or without metabolic activation. Oxymorphone hydrochloride tested positive in both the rat and mouse *in vivo* micronucleus assays. An increase in micronucleated polychromatic erythrocytes occurred in mice given doses ≥250 mg/kg and in rats given doses of 20 and 40 mg/kg. A subsequent study demonstrated that oxymorphone hydrochloride was not aneugenic in mice following administration of up to 500 mg/kg. Additional studies indicate that the increased incidence of micronucleated polychromatic erythrocytes in rats may be secondary to increased body temperature following oxymorphone administration. Doses associated with increased micronucleated polychromatic erythrocytes also produce a marked, rapid increase in body temperature. Pretreatment of animals with sodium salicylate minimized the increase in body temperature and prevented the increase in micronucleated polychromatic erythrocytes after administration of 40 mg/kg oxymorphone.

Impairment of fertility

Oxymorphone hydrochloride did not affect reproductive function or sperm parameters in male rats at any dose tested (≤50 mg/kg/day). The highest dose tested is ~6-fold the human dose of 40 mg every 12 hours, based on body surface area. In female rats, an increase in the length of the estrus cycle and decrease in the mean number of viable embryos, implantation sites and corpora lutea were observed at doses of oxymorphone ≥10 mg/kg/day. The dose of oxymorphone associated with reproductive findings in female rats is 1.2-fold the human dose of 40 mg every 12 hours based on a body surface area. The dose of oxymorphone that produced no adverse effects on reproductive findings in female rats is 0.6-fold the human dose of 40 mg every 12 hours on a body surface area basis.

14 CLINICAL STUDIES

The efficacy and safety of oxymorphone hydrochloride extended-release tablets have been evaluated in double-blind, controlled clinical trials in opioid-naïve and opioid-experienced patients with moderate to severe pain including low back pain.

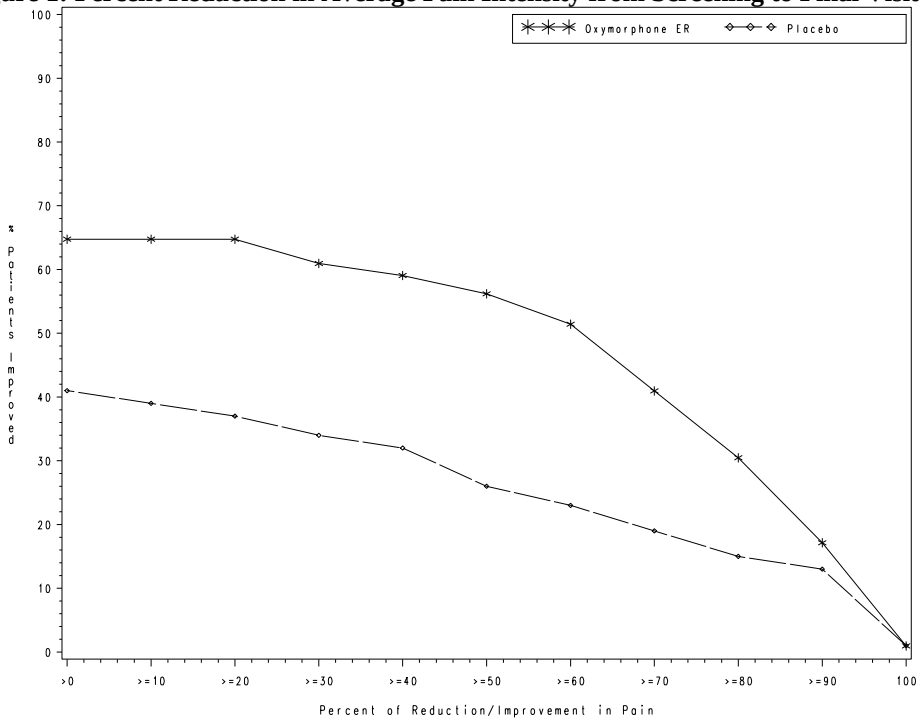
14.1 12-Week Study in Opioid-Naïve Patients with Low Back Pain

Patients with chronic low back pain who were suboptimally responsive to their current non-opioid therapy entered a 4-week, open-label dose titration phase. Patients initiated therapy with two days of treatment with oxymorphone hydrochloride extended-release tablets 5 mg, every 12 hours. Thereafter, patients were titrated to a stabilized dose, at increments of 5-10 mg every 12 hours every 3-7 days. Of the patients who were able to stabilize within the Open-Label Titration Period, the mean±SD VAS score at Screening was 69.4±11.8 mm and at Baseline (beginning of Double-Blind Period) were 18.5±11.2 mm and 19.3±11.3 mm for the oxymorphone ER and placebo groups, respectively. Sixty three percent of the patients enrolled were able to titrate to a tolerable dose and were randomized into a 12-week double-blind treatment phase with placebo or their stabilized dose of oxymorphone hydrochloride extended-release tablets. The mean±SD stabilized doses were 39.2±26.4 mg and 40.9±25.3 mg for the oxymorphone hydrochloride extended-release tablets and placebo groups, respectively; total daily doses ranged from 10-140 mg. During the first 4 days of double-blind treatment patients were allowed an unlimited number of OPANA, an immediate-release (IR) formulation of oxymorphone, 5 mg tablets, every 4-6 hours as supplemental analgesia; thereafter the number of OPANA was limited to two tablets per day. This served as a tapering method to minimize opioid withdrawal symptoms in placebo patients. Sixty-eight percent of patients

treated with oxymorphone hydrochloride extended-release tablets completed the 12-week treatment compared to forty seven percent of patients treated with placebo. Patients treated with oxymorphone hydrochloride extended-release tablets had a greater reduction in pain intensity than patients treated with placebo. The analgesic effect of oxymorphone hydrochloride extended-release tablets was maintained throughout the double-blind treatment period in 89% of patients who completed the study. These patients reported a decrease, no change, or a ≤10 mm increase in VAS score from Day 7 until the end of the study.

The proportion of patients with various degrees of improvement from screening to study endpoint is shown in Figure 1. The figure is cumulative, so that patients whose change from baseline is, for example, 30%, are also included at every level of improvement below 30%. Patients who did not complete the study were assigned 0% improvement.

Figure 1: Percent Reduction in Average Pain Intensity from Screening to Final Visit



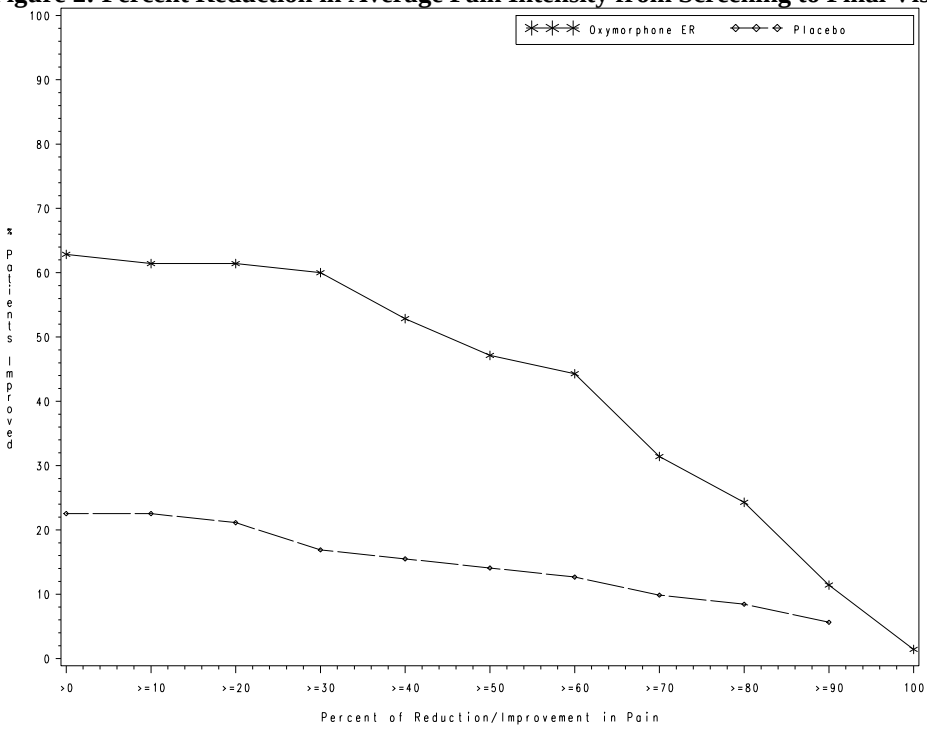
14.2 12-Week Study in Opioid-Experienced Patients with Low Back Pain

Patients currently on chronic opioid therapy entered a 4-week, open-label titration phase with oxymorphone hydrochloride extended-release tablets dosed every 12 hours at an approximated equianalgesic dose of their pre-study opioid medication. Of the patients who were able to stabilize within the Open-Label Titration Period, the mean±SD VAS score at Screening was 69.5±17.0 mm and at Baseline (beginning of Double-Blind Period) were 23.9±12.1 mm and 22.2±10.8 mm for the oxymorphone ER and placebo groups, respectively. Stabilized patients entered a 12-week double-blind treatment phase with placebo or their stabilized dose of oxymorphone hydrochloride extended-release tablets. The mean±SD stabilized doses were 80.9±59.3 mg and 93.3±61.3 mg for the oxymorphone hydrochloride extended-release tablets and placebo groups, respectively; total daily doses ranged from 20-260 mg. During the first 4 days of double-blind treatment, patients were allowed an unlimited number of OPANA 5 mg tablets, every 4-6 hours as supplemental analgesia; thereafter the number of OPANA was limited to two tablets per day. This served as a tapering method to minimize opioid withdrawal symptoms in placebo patients. Fifty seven percent of patients were titrated to a stabilized dose within approximately 4 weeks of oxymorphone hydrochloride extended-release tablets dose titration. Seventy percent of patients treated with oxymorphone hydrochloride extended-release tablets and 26% of patients treated with placebo completed the 12-week treatment. Patients treated with oxymorphone hydrochloride extended-release tablets had a greater reduction in pain intensity than patients treated with placebo. The analgesic effect of oxymorphone

hydrochloride extended-release tablets was maintained throughout the double-blind treatment period in 80 % of patients who completed the study. These patients reported a decrease, no change, or a ≤10 mm increase in VAS score from Day 7 until the end of the study.

The proportion of patients with various degrees of improvement from screening to study endpoint is shown in Figure 2. The figure is cumulative, so that patients whose change from baseline is, for example, 30%, are also included at every level of improvement below 30%. Patients who did not complete the study were assigned 0% improvement.

Figure 2: Percent Reduction in Average Pain Intensity from Screening to Final Visit



16 HOW SUPPLIED/STORAGE AND HANDLING

OPANA ER tablets are supplied as follows:

5 mg
Pink, round, film-coated, biconvex extended-release tablets debossed with an "E" on one side and a "5" on the other side.

Bottles of 60 with child-resistant closure	NDC 63481-434-60
Bottles of 100 with child-resistant closure	NDC 63481-434-70

7.5 mg
Gray, round, film coated, biconvex extended-release tablets debossed with an "E" on one side and a "7 ½" on the other side.

Bottles of 60 with child-resistant closure	NDC 63481-435-60
Bottles of 100 with child-resistant closure	NDC 63481-435-70

10 mg
Light orange, round, film-coated, biconvex extended-release tablets debossed with an "E" on one side and a "10" on the other side.

Bottles of 60 with child-resistant closure	NDC 63481-436-60
Bottles of 100 with child-resistant closure	NDC 63481-436-70

15 mg
White, round, film-coated, biconvex extended-release tablets debossed with an "E" on one side and a "15" on the other side.

Bottles of 60 with child-resistant closure	NDC 63481-437-60
Bottles of 100 with child-resistant closure	NDC 63481-437-70

20 mg
Light green, round, film-coated, biconvex extended-release tablets debossed with an "E" on one side and a "20" on the other side.

Bottles of 60 with child-resistant closure	NDC 63481-438-60
Bottles of 100 with child-resistant closure	NDC 63481-438-70

30 mg
Red, round, film-coated, biconvex extended-release tablets debossed with an "E" on one side and a "30" on the other side.

Bottles of 60 with child-resistant closure	NDC 63481-439-60
Bottles of 100 with child-resistant closure	NDC 63481-439-70

40 mg
Light yellow to pale yellow, round, film-coated, biconvex extended-release tablets debossed with an "E" on one side and a "40" on the other side.

Bottles of 60 with child-resistant closure	NDC 63481-440-60
Bottles of 100 with child-resistant closure	NDC 63481-440-70

OPANA ER contains oxymorphone, which is a controlled substance. Oxymorphone is controlled under Schedule II of the Controlled Substances Act. Oxymorphone, like all opioids, is liable to diversion and

misuse and should be handled accordingly. Patients and their families should be instructed to flush any OPANA ER tablets that are no longer needed.

OPANA ER may be targeted for theft and diversion. Healthcare professionals should contact their State Medical Board, State Board of Pharmacy or State Control Board for information on how to detect or prevent diversion of this product.

Healthcare professionals should advise patients to store OPANA ER in a secure place, preferably locked and out of the reach of children and other non-caregivers.

Store OPANA ER at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature].

Dispense in tight container as defined in the USP, with a child-resistant closure (as required).

Advise patients to dispose of any unused tablets from a prescription by flushing them down the toilet as soon as they are no longer needed *[see Patient Counseling Information (17)]*.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Medication Guide

- Advise patients that OPANA ER contains oxymorphone, a morphine-like pain medication, and should be taken only as directed.
- Advise patients that OPANA ER is designed to work properly only if swallowed whole. The extended-release tablets may release all their contents at once if broken, chewed or crushed, resulting in a risk of fatal overdose of oxymorphone.
- Advise patients they must not consume alcoholic beverages, or prescription or non-prescription medications containing alcohol, while on OPANA ER therapy. The co-ingestion of alcohol with OPANA ER may result in increased plasma levels and a potentially fatal overdose of oxymorphone.
- Advise patients that OPANA ER tablets should be taken on an empty stomach, **at least one hour prior to or two hours after eating**
- Advise patients that OPANA ER tablets should be taken one at a time.
- Advise patients not to pre-soak, lick or otherwise wet tablet prior to placing in the mouth.
- Advise patients to take each tablet with enough water to ensure complete swallowing immediately after placing in mouth.
- Appropriate pain management requires changes in the dose to maintain best pain control. Advise patients of the need to contact their physician if pain control is inadequate, but not to change the dose of OPANA ER without consulting their physician.
- Advise patients to report episodes of breakthrough pain and adverse experiences occurring during OPANA ER therapy to their doctor. Individualization of dosage is essential to make optimal use of this medication.
- Caution patients that OPANA ER may cause drowsiness, dizziness, or lightheadedness, and may impair mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car, operating machinery, etc.

- Instruct patients not to combine OPANA ER with central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because additive effects may occur, resulting in serious injury or death.

- Advise patients taking OPANA ER of the potential for severe constipation. Appropriate laxatives and/or stool softeners and other therapeutic approaches may be considered for use with the initiation of OPANA ER therapy.

- Advise patients not to adjust the dose of OPANA ER without consulting the prescribing professional.

- Advise patients that OPANA ER is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.

- Advise women of childbearing potential who become, or are planning to become pregnant to consult their physician regarding the effects of opioid analgesics and other drug use during pregnancy on themselves and their unborn child.

- Advise patients that if they miss a dose, to take it as soon as possible. If it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Advise patients not to take more than the prescribed dose of OPANA ER. If the patient is not sure about dosing advise them to call their healthcare provider.

- If patients have been receiving treatment with OPANA ER for more than a few days to weeks and cessation of therapy is indicated, counsel them on the importance of safely tapering the dose and that abruptly discontinuing the medication could precipitate withdrawal symptoms. Provide patients with a dose schedule to accomplish a gradual discontinuation of the medication.

- As with any potent opioid, misuse of OPANA ER may result in serious adverse events. Instruct patients to keep OPANA ER in a secure place out of the reach of children and pets. Accidental consumption especially in children can result in overdose or death. When OPANA ER is no longer needed, instruct patients to destroy unused tablets by flushing down the toilet.

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MEDICATION GUIDE

OPANA ER (Ō-pan-a) CII
(oxymorphone hydrochloride)
Extended-Release tablets

IMPORTANT: Keep OPANA ER in a safe place away from children. Accidental use by a child is a medical emergency and can result in death. If a child accidentally takes OPANA ER, get emergency help right away.

Read this Medication Guide completely before you start taking OPANA ER and each time you get a new prescription. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your

treatment. Be sure to share this important information with members of your household or other caregivers.

What is the most important information I should know about OPANA ER?

OPANA ER can cause serious side effects, including addiction or death.

1. **Take OPANA ER exactly as prescribed.** OPANA ER is not for use to treat pain that you only have now and then ("as needed"). Do not take OPANA ER for short term pain that you expect to go away in a few days, such as pain after surgery.
2. **Swallow OPANA ER tablets whole. Do not cut, break, crush, dissolve, or chew OPANA ER tablets before swallowing.** If OPANA ER is taken in this way, the medicine in the tablets will be released too fast. This is dangerous. It may cause you to have trouble breathing and lead to death. If you cannot swallow OPANA ER tablets whole, tell your healthcare provider. You may need a different medicine.
3. **Do not drink alcohol,** or take prescription or non-prescription medicines that contain alcohol while taking OPANA ER. Taking OPANA ER with alcohol may increase your risk of dangerous side effects and lead to death.
4. OPANA ER is a federally controlled substance (CII) because it is a strong opioid (narcotic) prescription pain medicine that can be misused by people who abuse prescription medicines or street drugs.
   - **Prevent theft, misuse or abuse. Keep OPANA ER in a safe place** to protect it from being stolen. OPANA ER can be a target for people who abuse opioid (narcotic) medicines or street drugs.
   - **Selling or giving away this medicine is against the law.**
   - **Never give OPANA ER to anyone else,** even if they have the same symptoms you have. It may harm them and even cause death.

What is OPANA ER?

- OPANA ER is a prescription medicine used to treat moderate to severe pain around-the-clock and is expected to last for a long period of time.
- OPANA ER is not for use:
  - to treat pain that you only have now and then "as needed".
  - right after surgery if the pain is mild or is not expected to last for a long period of time.
- Your healthcare provider may prescribe OPANA ER for pain after surgery if:
  - you were already taking OPANA ER before surgery, or
  - your pain after surgery is expected to be moderate or severe and last for a long period of time.

It is not known if OPANA ER is safe and effective in children under 18 years of age.

Who should not take OPANA ER?

Do not take OPANA ER if you:

- are allergic to oxymorphone or any of the ingredients in OPANA ER. See the end of this Medication Guide for a complete list of ingredients in OPANA ER.
- are allergic to codeine or other medicines that are like morphine. Ask your healthcare provider or pharmacist if you are not sure.
- are having an asthma attack or have severe asthma, trouble breathing, or lung problems.
- have a bowel blockage called a paralytic ileus.
- have liver problems.

What should I tell my healthcare provider before starting OPANA ER?

Before taking OPANA ER, tell your healthcare provider if you:

- have trouble breathing or lung problems
- have a head injury or brain problems
- have liver or kidney problems
- have adrenal gland problems, such as Addison's disease
- have convulsions or seizures
- have thyroid problems
- have severe scoliosis that affect your breathing
- have problems urinating or enlargement of your prostate
- have problems with your pancreas
- have a past or present drinking problem or alcoholism or a family history of this problem
- have severe mental problems or hallucinations (see or hear things that are not really there)
- have past or present drug abuse or drug addiction problems or a family history of this problem
- have any other medical problems
- **are pregnant or plan to become pregnant.** OPANA ER may harm your unborn baby.
- **are breastfeeding or plan to breastfeed.** It is not known if OPANA ER passes into your milk. Talk to your healthcare provider about the best way to feed your baby if you are taking OPANA ER.

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may cause serious or life-threatening medical problems when taken with OPANA ER. Your dose of OPANA ER may need to change if used with certain other medicines.

- Be especially careful about taking other medicines that may make you sleepy, such as:

- other pain medicines
- sleeping pills
- anti-anxiety medicines
- antihistamines
- anti-depressants
- tranquilizers
- anti-nausea medicine
- cimetidine (Tagamet)
- Monoamine Oxidase Inhibitors (MAOI). You should not take OPANA ER if you take a MAOI medicine or within 2 weeks of stopping an MAOI.

- **Do not take other medicines without talking to your healthcare provider or pharmacist. Your healthcare provider or pharmacist will tell you if it is safe to take other medicines while you take OPANA ER.**

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take OPANA ER?

- **Take OPANA ER exactly as prescribed.**
- Your healthcare provider will tell you how many OPANA ER tablets to take and when to take them.
- Do not change your dose unless your healthcare provider tells you to. **Do not take OPANA ER more often than prescribed.**
- Do not pre-soak, lick or get your OPANA ER wet before you place it in your mouth.
- Take 1 OPANA ER tablet at a time.
- Take each OPANA ER tablet with enough water to ensure the tablet is completely swallowed right after placing it in your mouth.
- **Swallow OPANA ER tablets whole.** Do not cut, break, crush, dissolve, or chew OPANA ER tablets. If OPANA ER is taken in this way, the medicine in the tablet will be released too fast. This is dangerous. It may cause you to have trouble breathing and lead to death.

  If you cannot swallow OPANA ER tablets whole, tell your healthcare provider. You may need a different medicine.
- Take OPANA ER on an empty stomach, at least 1 hour before meals or 2 hours after meals. Talk to your healthcare provider if you feel sick taking OPANA ER on an empty stomach.

- **If you miss a dose**, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. **Do not take more than your prescribed dose of OPANA ER.** If you are not sure about your dosing call your healthcare provider.

- If you take too much OPANA ER, call your healthcare provider or go to the nearest hospital emergency room right away.

- Talk to your healthcare provider regularly about your pain and tell your healthcare provider if you have pain that is not relieved with OPANA ER.

- **Stopping OPANA ER.** You should not stop taking OPANA ER suddenly if you have been taking it more than a few days, without talking to your healthcare provider. If your healthcare provider decides you no longer need OPANA ER, ask how to slowly stop your medicine so you do not get withdrawal symptoms such as nausea, sweating, and pain.

- **OPANA ER can cause physical dependence.** You can get sick with withdrawal symptoms if you stop OPANA ER suddenly, because your body has become used to it. Ask your healthcare provider if this is a concern for you.

What should I avoid while taking OPANA ER?

- **Do not drive, operate heavy machinery, or do other dangerous activities** until you know how OPANA ER affects you. OPANA ER can make you sleepy, and can make you feel dizzy or lightheaded. OPANA ER can also affect your ability to react. Ask your healthcare provider to tell you when it is okay to do these activities.

- **Do not drink alcohol or take prescription or non-prescription drugs that contain alcohol while taking OPANA ER.** Taking OPANA ER with alcohol may increase your risk of dangerous side effects and lead to death.

What are the possible side effects of OPANA ER?

OPANA ER can cause serious side effects, including:

- **See "What is the most important information I should know about OPANA ER?"**

- **Breathing problems. Call your healthcare provider or get medical help right away if:**
  - your breathing slows down
  - you have shallow breathing (little chest movement with breathing)
  - you feel faint, dizzy, confused, or have any other unusual symptoms

These can be signs or symptoms that you have taken too much OPANA ER (overdose) or the dose is too high for you. These symptoms may lead to serious problems or death if not treated right away.

- **Central nervous system effects.** OPANA ER can cause central nervous system effects, including sleepiness, dizziness, passing out or becoming unconscious (coma) and death, when taken with certain other medicines. See "What should I tell my healthcare provider before starting OPANA ER?"

- **Decreased blood pressure**. This can make you feel dizzy if you get up too fast from sitting or lying down. Low blood pressure is also more likely to happen if you are taking other medicines that can also lower your blood pressure. Severe low blood pressure can happen if you lost blood or take certain other medicines.

- **Physical Dependence**. Do not stop taking OPANA ER or any other opioid, without talking to your healthcare provider about how to slowly stop your medicine. If you have been taking OPANA ER for more than a few days, you could become sick with withdrawal symptoms if you stop taking it suddenly, because your body has become used to the medicine. Physical dependency is not the same as drug addiction.

- **The chance of abuse or addiction.** This chance is higher if you are or have ever been addicted to or abused other medicines, street drugs, or alcohol, or if you have a history of mental health problems. Abuse or addiction is different than a physical dependence. If you have more concerns, talk to your healthcare provider for more information about abuse and addiction.

The most common side effects of OPANA ER are:

- nausea
- constipation
- dizziness
- sleepiness
- vomiting
- itching
- headache
- increased sweating
- dry mouth
- sedation
- diarrhea
- trouble sleeping
- tiredness
- decreased appetite
- stomach (abdominal) pain

Constipation is a common side effect of opioid medicines, including OPANA ER. Talk to your healthcare provider or pharmacist about the use of laxatives and stool softeners to prevent or treat constipation while taking OPANA ER.

Talk to your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of OPANA ER. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store OPANA ER?

- **Keep OPANA ER in a safe place away from children and from anyone for whom it has not been prescribed.**
- Store OPANA ER at room temperature 68°F to 77°F (20°C to 25°C).
- Keep OPANA ER in the childproof container that it comes in.
- Flush unused OPANA ER tablets that are no longer needed down the toilet.

General information about OPANA ER

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use OPANA ER for a condition for which it was not prescribed. Never give OPANA ER to other people even if they have the same symptoms you have. **It may harm them and even cause death, and is against the law.**

This Medication Guide summarizes the most important information about OPANA ER. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about OPANA ER that is written for healthcare professionals. For more information about OPANA ER, go to www.endo.com or call 1-800-462-3636.

What are the ingredients in OPANA ER?
Active Ingredient: oxymorphone hydrochloride
Inactive Ingredients: hypromellose, polyethylene oxide, polyethylene glycol, α-tocopherol, citric acid, polyvinyl alcohol, titanium dioxide, macrogol and talc.

In addition, the:
5 mg, 7.5 mg and 30 mg tablets contain iron oxide red.
7.5 mg tablets contain iron oxide black, and iron oxide yellow.
10 mg tablets contain FD&C yellow No. 6.
20 mg tablets contain FD&C blue No. 1, FD&C yellow No. 6, and D&C yellow No. 10.
40 mg tablets contain FD&C yellow No. 6, and D&C yellow No. 10.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured for:
Endo Pharmaceuticals Inc., Chadds Ford, PA 19317

Manufactured by:
Pharmaceutical Manufacturing Research Services, Inc., Horsham, PA 19044

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